

TECHNICAL FIELD

5 carbostyryl derivatives represented by the following
general formula (I):



10 3- and 4-positions of the carbostyryl skeleton
represents a single bond or a double bond.

BACKGROUND ART

15 compound of the present invention, is known to be
useful as an antithrombotic agent, a cerebral

5

Oc1ccc2c(c1)c(cnc2=O)C3=CC=CC=C3 (II)
$$\begin{array}{c} \text{N} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{X}'-\text{A}-\text{C} \quad \text{N} \\ \diagdown \quad \diagup \\ \text{N} \\ | \\ \text{B} \end{array} \quad (\text{III}')$$

15 wherein X' represents a halogen atom, and A and R are as defined above, in the presence of an inorganic base or an organic base (see: JP-A-56-49378; USP No. 4,277,479; and Chem. Pharm. Bull., 31(4), 1151-1157 (1983)).

DISCLOSURE OF THE INVENTION

According to the above-mentioned known process, the yield of the compound of general formula (I) is as low as about 50 to 74%, because there is also
 5 formed a compound in which the tetrazole derivative of general formula (III') has reacted not only with the hydroxyl group of the carbostyryl derivative of general formula (II) but also with the 1-position of the carbostyryl derivative of general formula (II) simul-
 10 taneously. Since the thus formed contaminative impurity is difficult to remove, production of a compound of general formula (I) having a high purity has required a complicated process of purification.

It is an object of the present invention to
 15 provide a process for producing a carbostyryl derivative represented by the general formula (I) at a low cost and by a simple procedure. It is another object of the present invention to provide a process for producing a carbostyryl derivative represented by the
 20 general formula (I) without any complicated process of purification, in a high yield, and in a high purity. It is yet another object of the present invention to provide an industrially advantageous process for producing the carbostyryl derivatives represented by
 25 the general formula (I).

In view of the above-mentioned present situation, the present inventors have conducted various studies with the aim of achieving the above-mentioned

tetramethylene group.

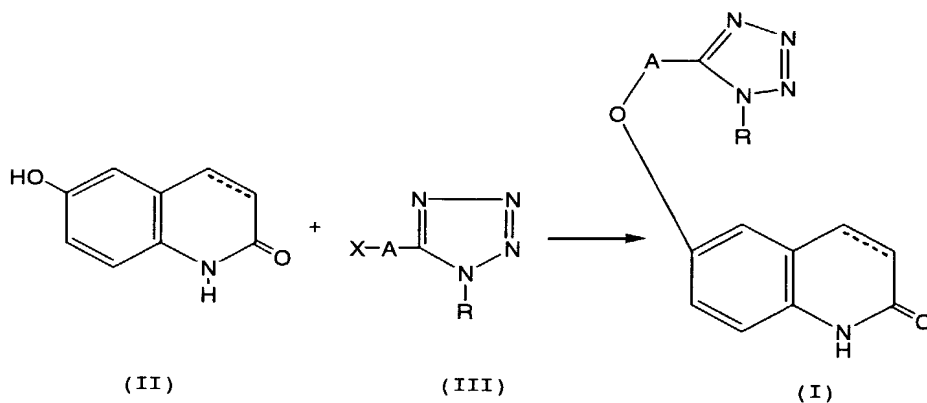
As the cycloalkyl group represented by R in the general formulas (I) and (III), mention can be made of, for example, cycloalkyl groups having 3-8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. Among these cycloalkyl groups, particularly preferred is cyclohexyl group.

As the halogen atom represented by X in the general formula (III), mention can be made of fluorine atom, chlorine atom, bromine atom and iodine atom, among which particularly preferred is chlorine atom.

As specific examples of the group causing the same substitution reaction as that caused by the halogen atom represented by X in the compound of general formula (III), mention can be made of lower alkanesulfonyloxy group, arylsulfonyloxy group, aralkylsulfonyloxy group and the like. As specific examples of the lower alkanesulfonyloxy group, mention can be made of methanesulfonyloxy, ethanesulfonyloxy, isopropanesulfonyloxy, propanesulfonyloxy, butanesulfonyloxy, tert-butanesulfonyloxy, pentanesulfonyloxy, hexanesulfonyloxy and the like. As specific examples of the arylsulfonyloxy group, mention can be made of substituted or unsubstituted arylsulfonyloxy groups such as phenylsulfonyloxy, 4-methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 3-

As the bond between the 3- and 4-positions of the carbostyryl skeleton in the general formulas (I) and (II), a single bond is particularly preferred.

15 Next, the process of the present invention will be explained in more detail with reference to reaction schemes.



20 wherein X, A, R and the bond between the 3- and 4-
positions of the carbostyryl skeleton are as defined

above.

In the reaction Scheme-1, the reaction between a compound of general formula (II) and a compound of general formula (III) is carried out in an appropriate solvent in the presence of a phase-transfer catalyst and further a basic compound. As the solvent used herein, all the inert solvents can be used so far as they exercise no adverse influence on the reaction. Examples of the solvent usable include water; alcohols such as methanol, ethanol, propanol, isopropyl alcohol, butanol, ethylene glycol and the like; ethers such as dimethyl ether, diethyl ether, diisopropyl ether, t-butyl methyl ether, tetrahydrofuran, dioxane, monoglyme, diglyme and the like; ketones such as acetone, methyl ethyl ketone, ethyl isobutyl ketone and the like; aromatic hydrocarbons such as benzene, o-dichlorobenzene, chlorobenzene, toluene, xylene and the like; esters such as methyl acetate, ethyl acetate, butyl acetate and the like; aprotic polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoramide and the like; and mixtures thereof. Among these solvents, particularly preferred are mixtures of water and an aromatic hydrocarbon such as benzene, o-dichlorobenzene, chlorobenzene, toluene, xylene and the like, and water itself alone.

As the basic compound, known ones can be used extensively. Examples thereof include inorganic bases such as sodium hydroxide, potassium hydroxide, cesium

dimethyloctylammonium chloride, methyltriethylammonium chloride, benzylmethyloctadecanyleammonium chloride, methyltridecanyleammonium chloride, benzyltripropyleammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride and the like; phosphonium salts substituted with a residue selected from the group consisting of straight or branched chain alkyl groups having 1-18 carbon atoms such as tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched chain alkyl group having 1-18 carbon atoms such as 1-dodecanylepyridinium chloride and the like. Among these phase transfer catalysts, quaternary ammonium salts substituted with a straight or branched chain alkyl group having 1-18 carbon atoms such as tetrabutyleammonium chloride and the like are particularly preferred. As the salt-forming ions in these salts, hydroxyl ion, hydrogen sulfate ion and halogen ions are preferred, among which chlorine ion is particularly preferred. If desired, sodium sulfite or the like may be added to the reaction system of the above-mentioned reaction for the purpose of preventing the coloration caused by oxidation.

25 The reaction is carried out usually at a temperature not lower than ambient temperature and not higher than 200°C, and preferably at a temperature of 50-150°C. The reaction time is usually from about one

hour to about 10 hours. It is recommended to use the compound (III) usually in an amount of at least 0.5 mol and preferably 0.5-1.5 mol per mol of the compound (II), to use the basic compound usually in an amount of 1-5 mol per mol of the compound (II), and to use the phase transfer catalyst usually in an amount of 0.1-1 mol and preferably 0.1-0.5 mol per mol of the compound (II).

The compound of general formula (I) obtained by the above-mentioned reaction can easily be isolated by the conventional separating means. As said separating means, mention can be made of, for example, extraction method using a solvent, dilution method, recrystallization method, column chromatography, preparative thin layer chromatography, etc.

Examples

Next, the process of the present invention is more concretely explained below with reference to examples. The invention is by no means limited thereby.

Example 1

Into a three-necked flask having a capacity of 300 ml were introduced 10.00 g of 6-hydroxy-3,4-dihydrocarbostyryl, 16.36 g of 1-cyclohexyl-5-(4-chlorobutyl)-1,2,3,4-tetrazole, 10.16 g of potassium carbonate, 3.00 g of tetrabutylammonium chloride, 0.05 g of sodium sulfite, 30 ml of toluene and 50 ml of

water. The content of the flask was heated under reflux for 8 hours. After cooling the reaction mixture to ambient temperature, the deposited crystalline product was collected by filtration and washed with 50 ml of water. Then, the crude crystal thus obtained was introduced into 70 ml of 90% methanol cooled to 5°C, and stirred at 5°C for 10 minutes for the sake of washing. The crystal was collected by filtration and further washed on the suction filter with 20 ml of 90% methanol cooled to 5°C. The crystal was dried to obtain 21.46 g (yield 95%) of 6-[4-(1-cyclohexyl-1,2,3,4-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyryl as a colorless needle-like crystalline product.

Purity: 99.80%; m.p.: 158-159°C

The purity was measured by high performance liquid chromatography under the following conditions:

Column: YMC Pack SIL A-002 (manufactured by YMC Co.)

Moving phase: dichloromethane/n-hexane/methanol=
20/10/1

Detector: UV, 254 nm

Flow rate: 0.90 ml/min.

Retention time: 4.7 min.

Example 2

Into a flask having a capacity of 200 ml were introduced 12.00 g of 6-hydroxy-3,4-dihydrocarbostyryl, 19.60 g of 1-cyclohexyl-5-(4-chlorobutyl)-1,2,3,4-tetrazole, 8.20 g of 50% aqueous solution of

tetrabutylammonium chloride, 12.20 g of potassium carbonate, 0.60 g of sodium sulfite and 60 ml of water. The content of the flask was heated under reflux for 8 hours with stirring. After the reaction, the reaction mixture was cooled to ambient temperature, and the deposited crude crystal was once collected by filtration. After washing the crystal firstly with 36 ml of methanol and then with 60 ml of water, the crystal was again introduced into a flask having a capacity of 200 ml and heated under reflux together with 84 ml of methanol for 2 hours. The solution thus obtained was cooled to 10°C. The crystal was collected by filtration, washed firstly with 24 ml of methanol and then with 24 ml of water, and dried at 80°C. Thus, 23.84 g (yield 87.7%) of 6-[4-(1-cyclohexyl-1,2,3,4-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyryl was obtained as a colorless needle-like crystalline product.

Purity: 99.89%; m.p.: 158–159°C

The purity was measured by high performance
20 liquid chromatography (HPLC) under the same conditions
as in Example 1.